

# **EXHIBIT D**

# Health Effects of Energy Drinks on Children, Adolescents, and Young Adults

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**KEY WORDS**

energy drink, caffeine, taurine, children, adolescents, overdose

**ABBREVIATIONS**

FDA—Food and Drug Administration

ADHD—attention-deficit/hyperactivity disorder

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## abstract

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**OBJECTIVE:** To review the effects, adverse consequences, and extent of energy drink consumption among children, adolescents, and young adults.

**METHODS:** We searched PubMed and Google using “energy drink,” “sports drink,” “guarana,” “caffeine,” “taurine,” “ADHD,” “diabetes,” “children,” “adolescents,” “insulin,” “eating disorders,” and “poison control center” to identify articles related to energy drinks. Manufacturer Web sites were reviewed for product information.

**RESULTS:** According to self-report surveys, energy drinks are consumed by 30% to 50% of adolescents and young adults. Frequently containing high and unregulated amounts of caffeine, these drinks have been reported in association with serious adverse effects, especially in children, adolescents, and young adults with seizures, diabetes, cardiac abnormalities, or mood and behavioral disorders or those who take certain medications. Of the 5448 US caffeine overdoses reported in 2007, 46% occurred in those younger than 19 years. Several countries and states have debated or restricted energy drink sales and advertising.

**CONCLUSIONS:** Energy drinks have no therapeutic benefit, and many ingredients are understudied and not regulated. The known and unknown pharmacology of agents included in such drinks, combined with reports of toxicity, raises concern for potentially serious adverse effects in association with energy drink use. In the short-term, pediatricians need to be aware of the possible effects of energy drinks in vulnerable populations and screen for consumption to educate families. Long-term research should aim to understand the effects in at-risk populations. Toxicity surveillance should be improved, and regulations of energy drink sales and consumption should be based on appropriate research. *Pediatrics* 2011;127:511–528

"Energy drinks" are beverages that contain caffeine, taurine, vitamins, herbal supplements, and sugar or sweeteners and are marketed to improve energy, weight loss, stamina, athletic performance, and concentration.<sup>1–3</sup> Energy drinks are available in >140 countries and are the fastest growing US beverage market; in 2011, sales are expected to top \$9 billion.<sup>4–10</sup> Half of the energy drink market consists of children (<12 years old), adolescents (12–18 years old), and young adults (19–25 years old).<sup>7–10</sup>

Although healthy people can tolerate caffeine in moderation, heavy caffeine consumption, such as drinking energy drinks, has been associated with serious consequences such as seizures, mania, stroke, and sudden death.<sup>6–8,11–14</sup> Numerous reports exist in the popular media, and there are a handful of case reports in the literature that associate such adverse events with energy drink consumption; it is prudent to investigate the validity of such claims (Appendix). Children, especially those with cardiovascular, renal, or liver disease, seizures, diabetes, mood and behavioral disorders, or hyperthyroidism or those who take certain medications, may be at higher risk for adverse events from energy drink consumption.<sup>6–8,14–24</sup> Although the US Food and Drug Administration (FDA) limits caffeine content in soft drinks, which are categorized as food, there is no such regulation of energy drinks, which are classified as dietary supplements.<sup>1–3</sup> Despite the large, unregulated market for energy drinks and reports in the literature and popular media of serious adverse events associated with their consumption, research into their use and effects has been sparse.<sup>25</sup> However, schools, states, and countries increasingly are exploring content and sales regulations of these drinks.<sup>1,8,13,26–35</sup>

Given the rapidly growing market and popularity among youth, we reviewed the literature to (1) determine what energy drinks are, (2) compile consumption data of energy drinks by children, adolescents, and young adults, (3) compile caffeine and energy drink overdose data, (4) examine the physiologic effects of the ingredients in energy drinks, (5) identify potential problems of energy drinks among children and adolescents, (6) assess the marketing of energy drinks, (7) report current regulation of energy drinks, and (8) propose educational, research, and regulatory recommendations.

## METHODS

We searched PubMed by using "energy drink," "sports drink," "guarana," "caffeine," "taurine," "ADHD" (attention-deficit/hyperactivity disorder), "diabetes," "children," "adolescents," "insulin," "eating disorders," and "poison control center" singly or in combination. We limited searches to English-language and foreign-language articles with English-language abstracts and selected articles by relevance to energy drink use in children and adolescents. We similarly searched Google for print and trade media. We reviewed articles and Internet sources by the above search through June 2010 and updated sections as new information became available through January 2011.

## RESULTS

Two-thirds of the 121 references we found on energy drinks were in the scientific literature, although reports by government agencies and interest groups also contained much useful information (Table 1). Most information came from the United States, but European, Canadian, Australian, New Zealand, and Chinese sources are also represented.

## DISCUSSION

### What Are Energy Drinks?

Energy drinks may contain caffeine, taurine, sugars and sweeteners, herbal supplements, and other ingredients (Table 2) and are distinct from sports drinks and vitamin waters (Table 3).<sup>6,8</sup> In 2008, the National Federation of State High School Associations, while recommending water and sports drinks for rehydration, specifically did not recommend energy drinks and cited potential risks, the absence of benefit, and drug interactions (Table 4).<sup>36,37</sup>

Caffeine is the main active ingredient in energy drinks; many of them contain 70 to 80 mg per 8-oz serving (~3 times the concentration in cola drinks) (Table 5).<sup>8,31</sup> Caffeine content can be nearly 5 times greater than that in 8 oz of cola drinks when packaged as "energy shots" (0.8–3 oz) or as 16-oz drinks.<sup>6,29,38</sup>

Energy drinks often contain additional amounts of caffeine through additives, including guarana, kola nut, yerba mate, and cocoa.<sup>6,7,14,25</sup> Guarana (*Paullinia cupana*) is a plant that contains caffeine, theobromine (a chronotrope), and theophylline (an inotrope).<sup>7,8,14,39</sup> Each gram of guarana can contain 40 to 80 mg of caffeine, and it has a potentially longer half-life because of interactions with other plant compounds.<sup>7,14</sup> Manufacturers are not required to list the caffeine content from these ingredients.<sup>7,14</sup> Thus, the actual caffeine dose in a single serving may exceed that listed.<sup>9,29</sup>

### Consumption of Energy Drinks by Children, Adolescents, and Young Adults

In the United States, adolescent caffeine intake averages 60 to 70 mg/day and ranges up to 800 mg/day.<sup>24,40</sup> Most caffeine intake among youth comes from

**TABLE 1** Primary Literature and Media Sources Selected for Review, According to Relevance

Source Description	No. of Results	Main Topics	Source Country
Primary literature	81	—	—
Systematic reviews	0	—	—
Review articles	36	Energy drinks are a growing problem; safety issues with energy drinks; stimulant adverse effects; caffeine dependence; caffeine and fluid-electrolyte balance; caffeine and exercise performance; caffeine and mental performance; caffeine and apnea of prematurity; caffeine and bronchopulmonary dysplasia; caffeine and coronary heart disease; herb adverse effects; adolescents with ADHD and misuse of medication; ADHD and substance use; cardiovascular effects of antidepressants in children and adolescents; caffeine consumption and eating disorders; caffeine and bone gain in children and adolescents; incidence of pediatric cardiomyopathy; frequency of myocardial injury in children; epidemiology of hypertrophic cardiomyopathy	US, Poland, United Kingdom, Germany, China
Randomized controlled trials	0	—	—
Experimental studies	16	Cognitive and physiological effects of energy drinks; caffeine and exercise performance, thermoregulation, and fluid-electrolyte balance; energy drink effects on hemodynamic and electrocardiographic parameters in young adults; caffeine effects in children; gender differences and caffeinated beverages; taurine and cardiac parameters; energy drinks and platelet and endothelial function; eye-tracking in adolescents viewing advertisements	United States, United Kingdom, Germany
Cohort studies	2	Caffeine and sleep patterns in children; caffeine exposure in children, adolescents, and young adults	United States
Surveys	4	Consumption by college students; consumption of caffeinated beverages by adolescents; energy drinks and risk-taking behavior; survey of obstetrician/gynecologist caffeine knowledge	United States, Germany
Case reports	8	Caffeine-induced psychosis; energy drinks and seizures; cardiac arrest after energy drink consumption; cardiac arrhythmias associated with energy drink consumption; caffeine fatalities; Red Bull and postural tachycardia; cardiomyopathy and pericarditis after methylphenidate; psychosis after energy drink consumption	United States
Perspectives	10	Caution reduces long-term health risks; pediatric cardiology; cardiovascular adverse effects of stimulants; prevention of hypertension; stimulants and sudden death; cardiovascular disease and stimulants in children; sugary beverages and childhood obesity; fluid replacement and exercise	United States
Basic science	5	Stimulants and insulin-stimulated glucose uptake in rats; adenosine receptors in rats; structural changes in rat heart tissue after oral methylphenidate	United States
Animal studies	3	Stimulants and insulin-stimulated glucose uptake in rats; adenosine receptors in rats; structural changes in rat heart tissue after oral methylphenidate	United States
Human studies	2	Caffeine modulates gene expression; guarana and platelet function	United States
Government agency reports	10	FDA overview of dietary supplements; energy drinks/high-caffeine beverages; caffeinated beverages and obesity; dietary supplements and military personnel; German assessment of energy drinks; Canadian assessment of energy drinks; health risks of energy shots; Poison Control Center data	Australia, Canada, European Germany, New Zealand, United States
Interest groups	3	Alcoholic energy drinks and youth; nutrition and energy drinks	United States
Popular media	27	Overuse of energy drinks and health consequences; school bans on energy drinks; racial differences in caffeine metabolism; energy drink dangers for youth; restriction of drugs in youth; preparticipation screening and congenital heart defects; regulation of energy drinks; Hong Kong's ban of Red Bull; questioning dietary supplements	United States
Newspaper articles	14	Overuse of energy drinks and health consequences; school bans on energy drinks; racial differences in caffeine metabolism; energy drink dangers for youth; restriction of drugs in youth; preparticipation screening and congenital heart defects; regulation of energy drinks; Hong Kong's ban of Red Bull; questioning dietary supplements	United States
Web sites	12	Energy drink sales; French ban on Red Bull; Germany questions energy drink safety; a school's ban on energy drinks; marketing of energy drinks; high caffeine levels in energy drinks in Australia; Ireland's review of the safety of energy drinks; Dutch schools' ban on Red Bull; preparticipation sports physicals	Holland, United Kingdom, United States
Books	1	History of energy drinks and health consequences	United States
Total	121		

**TABLE 2** Common Ingredients, Therapeutic Uses, and Adverse Effects of Energy Drink Ingredients<sup>8,14,25,30,49,53,82,83</sup>

Ingredient	Description	Therapeutic Uses	Purported Effect From Energy Drinks	Adverse Effects (due to Idiosyncratic Reaction or Excessive Dosage)
Caffeine	An adenosine receptor antagonist: a central nervous system stimulant	As caffeine citrate, used to treat apnea and bronchopulmonary dysplasia in premature infants	Increases exercise endurance and improves cognition and mood when fatigued or sleep-deprived	Nervousness, irritability, anxiety, insomnia, tachycardia, palpitations, upset stomach, vomiting, abdominal pain, rigidity, hypokalemia, altered consciousness, paralysis, hallucinations, increased intracranial pressure, cerebral edema, seizures, rhabdomyolysis, supraventricular and ventricular tachyarrhythmias
Guarana	A South American plant that contains large amounts of caffeine, theobromine, and theophylline (a chronotrope and an inotrope) and tannins	None known	Stimulant, mainly through the effects of caffeine, and weight loss	Generally considered safe by the FDA Center for Food Safety and Applied Nutrition
Taurine	An abundant amino acid in the central nervous system; acts in neural growth and protection, cell metabolism, osmoregulation, antioxidation, and glycolysis; estimated daily intake is 400 mg/d	Infant formula has been supplemented with taurine since the 1980s because of evidence that it promotes healthy development; used to treat alcohol withdrawal, congestive heart failure, cystic fibrosis, palpitations/dysrhythmias, hypertension, diabetes, seizure disorders, hepatitis	Marketed to promote eye and biliary health and to prevent congestive heart failure by lowering blood pressure while improving cardiac contractility	Generally considered safe by the FDA
L-Carnitine	An amino acid involved in $\beta$ -oxidation of fatty acids	Used as a therapeutic supplement in congenital and acquired-deficiency states, end-stage renal disease, valproate toxicity, and dementia; increases attention and decreases hyperactivity in certain populations of children; nonstimulant L-acetyl-carnitine is used to treat ADHD in boys with fragile X syndrome and, in 1 study, children with typical ADHD; it may also protect against heart disease	Added to promote fat metabolism and increase endurance	In high doses, can cause nausea, vomiting, abdominal pain, and diarrhea; has been reported to cause seizures in patients with no known disease and to increase seizure frequency in patients with seizure disorder
Ginseng	An East Asian herb	Believed to improve memory, increase stamina, and stimulate immune function	Improve physical performance	Reported symptoms of ginseng toxicity include diarrhea, vaginal bleeding, headache, vertigo, mania, hypertension, rashes, insomnia, irritability, Stevens-Johnson syndrome, and agranulocytosis; some of these symptoms may be related to contaminants, such as phenylbutazone and aminopyrine, used in its processing
Yohimbine	An alkaloid found in the plants <i>Pausinystalia yohimbe</i> and <i>Rauwolfia serpentina</i>	An herbal supplement believed to be an aphrodisiac and to relieve chest pain, diabetic complications, depression, and erectile dysfunction	Increase energy, metabolism, and stamina; promotes well-being	Can cause hypertension at usual doses and hypotension at high doses; tachycardia, death

soda; however, energy drinks are becoming increasingly popular.<sup>7,24,41,42</sup> Several self-report studies have examined energy drink consumption by children, adolescents, and young adults.<sup>7,24,41,42</sup>

One study found that 28% of 12- to 14-year-olds, 31% of 12- to 17-year

olds, and 34% of 18- to 24-year-olds reported regularly consuming energy drinks.<sup>5,43</sup> Shortly after energy drinks were approved in Germany, a study of 1265 adolescents found that 94% were aware of energy drinks, 53% had tried them, 23% drank <1

cans per week, and 3% drank 1 to 7 cans per week.<sup>44</sup> Among 10- to 13-year-olds, 31% of girls and 50% of boys had tried energy drinks, and 5% of girls and 23% of boys reported drinking them regularly but at a rate of <1 can per week.<sup>44</sup> Most children

**TABLE 3** Characteristics of Sports Drinks, Vitamin Drinks, and Energy Drinks<sup>1,4,8,14,37,115,117</sup>

	Sports Drinks	Enhanced/Fortified Vitamin Waters	Energy Drinks
Common brand names	Gatorade; Powerade	Glacéau Vitamin Water; SoBe Lifewater; Dasani Plus	Red Bull, Full Throttle, Monster Energy, Rockstar
Advertised purpose	To rehydrate the body after intense exercise for $\geq 1$ h	Broad claims that range from improving endurance to strengthening immune defense to relaxation	To rapidly increase energy, endurance, and performance
Ingredients	Glucose, electrolytes	Water, vitamins, nutrients, sometimes sweeteners; no stimulants	Caffeine, sugar, herbal supplements, other substances (eg, taurine, glucuronolactone)
Effects	Replaces lost electrolytes and carbohydrates during sustained strenuous exercise; prevents dehydration	Prevents dehydration; may replace some nutrients; other than the caloric sweeteners, the contents are unlikely to present health risks, and there is no published evidence of benefit	Temporarily increases heart and respiratory rates and blood pressure; not designed to hydrate the body

**TABLE 4** Potential Pharmaceutical Supplement Interactions With Energy Drink Ingredients<sup>30,82,83</sup>

Energy Drink Ingredient	Interactions
5-Hydroxy tryptophan	Should not be combined with monoamine oxidase inhibitors
Vinpocetine	Increases the risk for excessive bleeding and should not be combined with aspirin, clopidogrel, warfarin, pentoxifylline, vitamin E, garlic, and gingko
Yohimbine	Affects cardiac function and should not be combined with tricyclic antidepressants, bupropion, phenothiazines, clonidine, stimulants, decongestants, or other blood pressure-lowering medications
Ginseng	Prolongs bleeding time and should not be combined with warfarin; interacts with phenelzine sulfate in patients being treated for mania; may interfere with estrogens or corticosteroids; may impede digoxin metabolism; reduces blood glucose levels

**TABLE 5** Caffeine Content Reported by Manufacturers and Selected Additional Ingredients of Selected Products<sup>6,29,46</sup>

Product	Selected Ingredients	Sugar Content per 8 oz, g	Average Caffeine Dose per 8 oz, mg	Amount per Serving, oz	Average Caffeine Dose per Container, mg
Comparison products					
NoDoz	Caffeine	0	NA <sup>a</sup>	NA <sup>a</sup>	200 mg per tablet
Excedrin	Acetaminophen, aspirin, caffeine	0	NA <sup>a</sup>	NA <sup>a</sup>	65 mg per tablet (serving size: 2 tablets)
Hershey's Kisses	Caffeine, sugar	21 in 9 pieces	NA <sup>a</sup>	NA <sup>a</sup>	9 mg in 9 pieces
Coca-Cola	Caffeine, sugar	19–25	23	12	35
Mountain Dew	Caffeine, sugar	32	28	16	55
Diet Pepsi Max	Ginseng	0	47	12	69
Tea, brewed	NA <sup>a</sup>	0	54	8	54
Coffee, generic brewed	NA <sup>a</sup>	0	100	8	100
Starbucks tall coffee	NA <sup>a</sup>	0	174	12	260
Energy drinks					
Low calorie	B vitamins, dextrose, fumarate, gingko, ginseng, glucuronolactone, guarana, glucose, inositol, L-arginine, L-carnitine, milk thistle, n-acetyl-L-tyrosine, sucrose, taurine, yohimbine HCL, vinpocetine, 5-hydroxy tryptophane	0	77–19 200	0.17–16.00	80–400
Regular	B vitamins, dextrose, fumarate, gingko, ginseng, glucuronolactone, guarana, high-fructose corn syrup, glucose, inositol, L-arginine, L-carnitine, milk thistle, n-acetyl-L-tyrosine, sucrose, taurine, yohimbine HCL, vinpocetine, 5-hydroxy tryptophane	17–30	71–286	8.3–16.0	75–300
Super-caffeinated	B vitamins, dextrose, fumarate, gingko, ginseng, glucuronolactone, guarana, glucose, inositol, L-arginine, L-carnitine, milk thistle, n-acetyl-L-tyrosine, sucrose, taurine, yohimbine HCL, vinpocetine, 5-hydroxy tryptophane	0	315–19 200	0.17–2.50	80–400

NA indicates not applicable.

<sup>a</sup> Product-specific information is from company Web sites; ingredients may vary according to country.

in the study consumed energy drinks in moderation, but a small group consumed extreme amounts.<sup>44</sup>

A survey of 496 college students found that 51% of those surveyed regularly consumed  $>1$  energy drink per

month; the majority of them habitually drank energy drinks several times per week.<sup>9</sup> Insufficient sleep (67%) and the

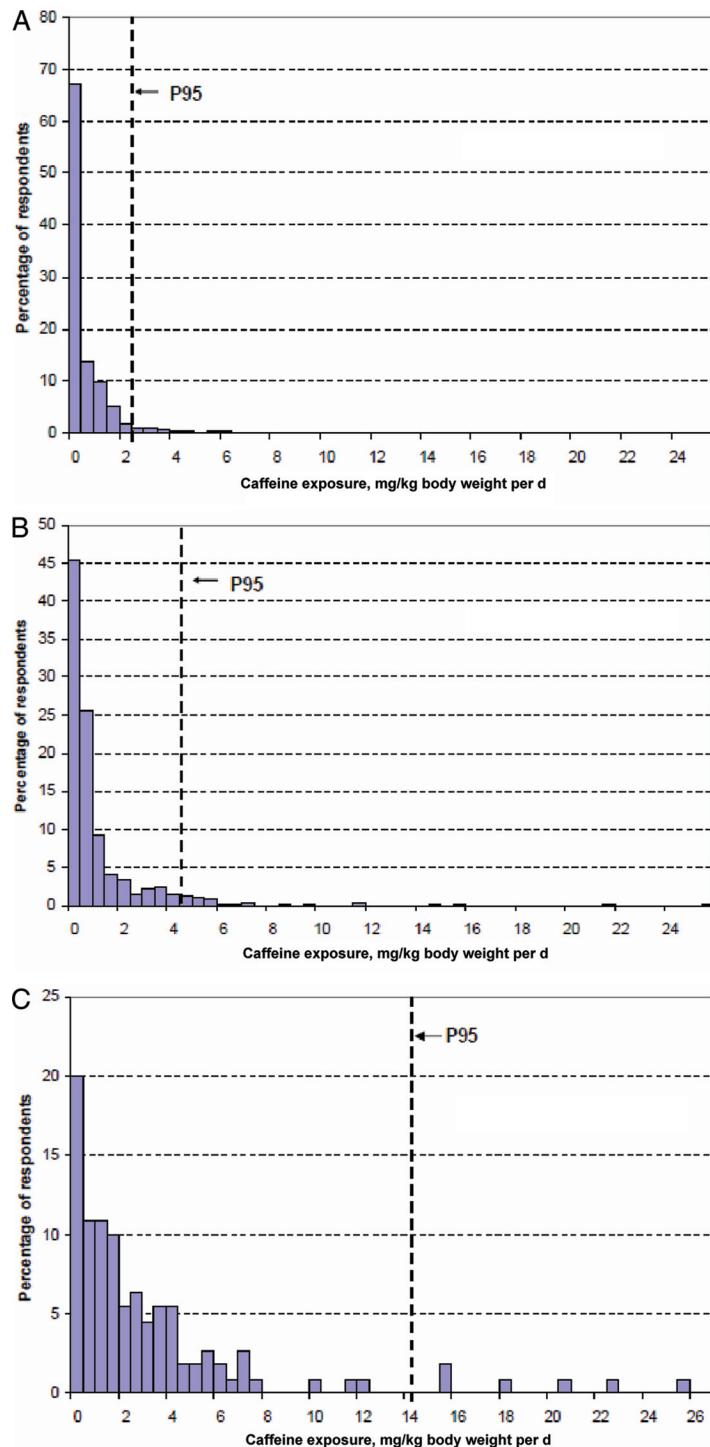
desire to increase energy (65%) were the most common reasons for use.<sup>9</sup> In this study, 54% of the respondents reported mixing energy drinks with alcohol, and 49% drank  $\geq 3$  of them while partying.<sup>9</sup> Another study of 795 college students found that 39% of the respondents had consumed an energy drink in the previous month and that, on average, men drank energy drinks 2.5 days/month, whereas women drank 1.2 days/month.<sup>45</sup>

The estimated caffeine exposure of consuming energy drinks or energy shots was calculated for New Zealand children (5–12 years old), teenagers (13–19 years old), and young men (19–24 years old) (Figs 1–3).<sup>46</sup> After consuming a single retail unit, 70% of the children and 40% of the teenagers who consumed caffeine were estimated to have exceeded the adverse-effect level of 3 mg/kg body weight per day beyond their baseline dietary exposure.<sup>46</sup> An average child, teenager, or young man would all, on average, exceed the adverse-effect level after consuming a single retail unit of energy drink/energy shot above their baseline dietary caffeine exposure.<sup>46</sup>

### Caffeine and Energy Drink Overdoses

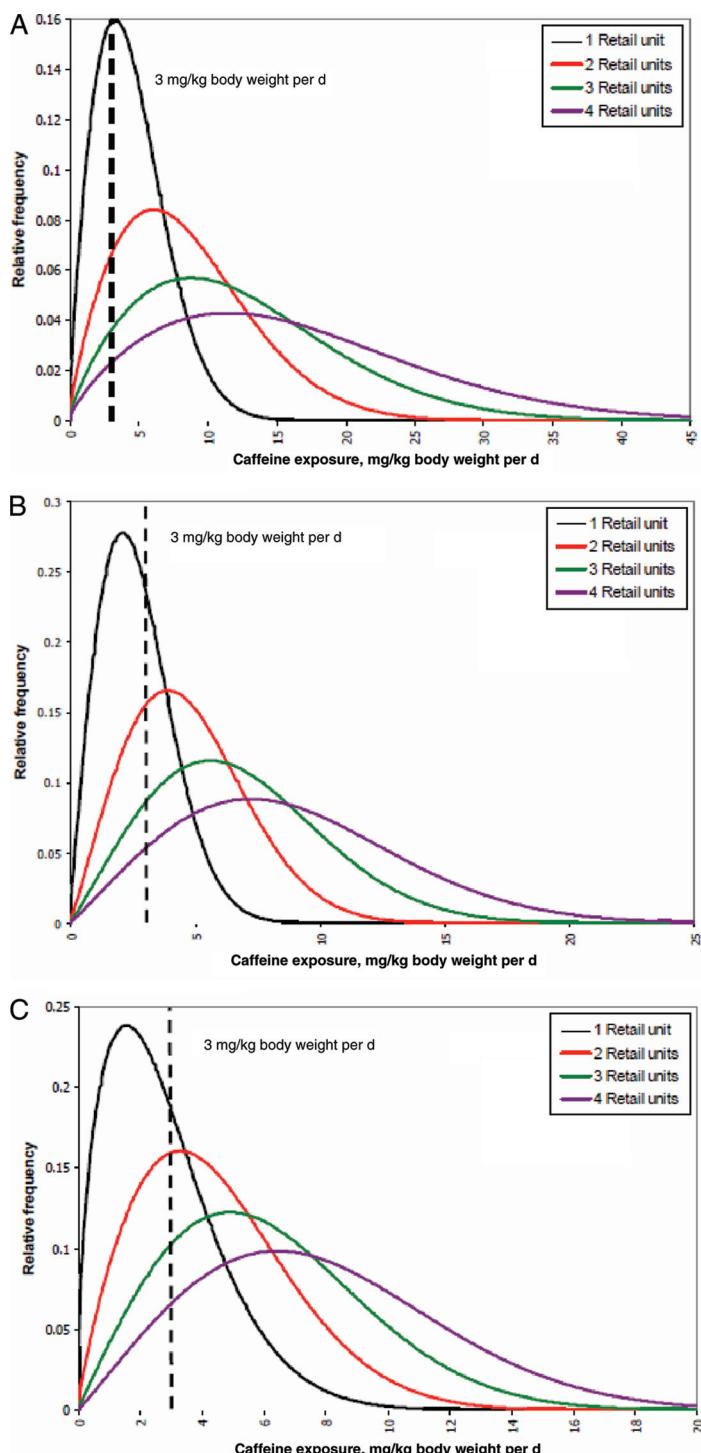
US poison control centers have not specifically tracked the prevalence of overdoses attributed to energy drinks, because exposures were coded as “caffeine” or “multisubstance exposures” and combined with other caffeine sources (Table 6) (American Association of Poison Control Centers Board of Directors, personal communication, 2010).<sup>47</sup> Energy drinks were recently given unique reporting codes, so their toxicity can now be tracked (American Association of Poison Control Centers Board of Directors, personal communication, 2010).<sup>47</sup>

Germany has tracked energy drink-related incidents since 2002.<sup>33</sup> Re-



**FIGURE 1**

Mathematical model estimates for dietary consumption of caffeine and energy drinks in children aged 5 to 12 years (A), adolescents aged 13 to 19 years (B), and young males aged 19 to 24 years (C) using caffeine-concentration data from food and beverages combined with 24-hour diet-recall information from the 1997 New Zealand National Nutrition Survey and the 2002 New Zealand National Children's Nutrition Survey. A, Distribution of dietary baseline caffeine-exposure estimates for children (5–12 years old).<sup>46</sup> P95 indicates the 95th percentile exposure and represents a high consumer. Caffeine-exposure units are mg/kg of body weight per day. B, Distribution of dietary baseline caffeine-exposure estimates for teenagers (13–19 years old).<sup>46</sup> C, Distribution of dietary baseline caffeine-exposure for young males (19–24 years old).<sup>46</sup> Reproduced with permission from David Crowe, manager of consumer communications for the New Zealand Food Safety Authority.

**FIGURE 2**

A, Estimated distribution of caffeine exposure for children (5–12 years old) after the consumption of 1 to 4 retail units of energy drinks or energy shots.<sup>46</sup> B, Estimated distribution of caffeine exposure for teenagers (13–19 years old) after the consumption of 1 to 4 retail units of energy drinks or energy shots.<sup>46</sup> C, Estimated distribution of caffeine exposure for young males (19–24 years old) after the consumption of 1 to 4 retail units of energy drinks or energy shots.<sup>46</sup> Caffeine-exposure units are mg/kg body weight per day. An adverse effect level of 3 mg/kg body weight per day is shown as a basis for risk evaluation. The area under the curves to the right of the adverse-effect lines represents the proportion of consumers potentially at risk from adverse effects of caffeine or the probability of a random consumer exceeding the adverse-effect level. Reproduced with permission from David Crowe, manager of consumer communications for the New Zealand Food Safety Authority.

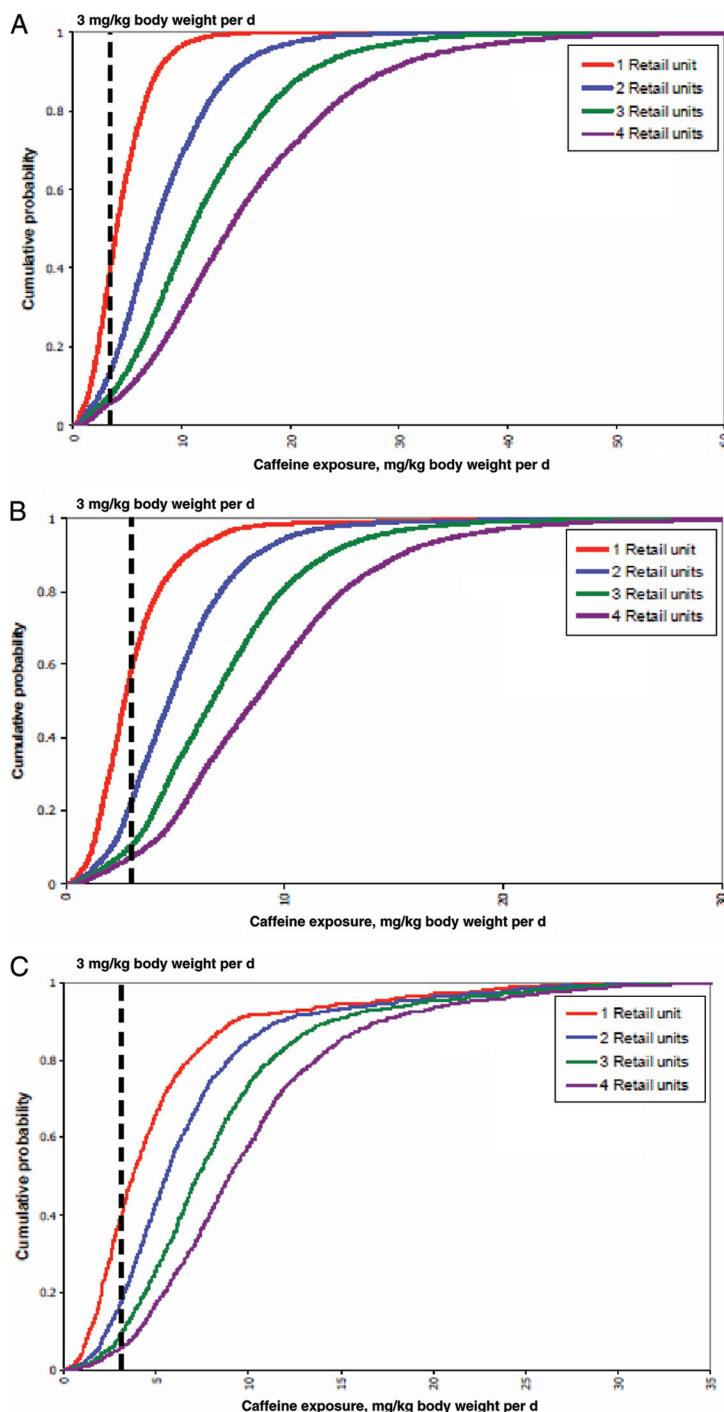
ported outcomes include liver damage, kidney failure, respiratory disorders, agitation, seizures, psychotic conditions, rhabdomyolysis, tachycardia, cardiac dysrhythmias, hypertension, heart failure, and death.<sup>33</sup> Ireland's poison center reported 17 energy drink adverse events including confusion, tachycardia, and seizures and 2 deaths between 1999 and 2005.<sup>25</sup> New Zealand's poison center reported 20 energy drink/shot-related adverse events from 2005 to 2009; 12 cases were referred for treatment of vomiting, nausea, abdominal pain, jitteriness, racing heart, and agitation.<sup>46</sup> The minimum and maximum symptomatic caffeine levels were 200 mg (4 mg/kg) in a 13-year-old with jitteriness and 1622 mg (35.5 mg/kg) in a 14-year-old. The maximum volume consumed was fifteen 250-mL cans (11.5 mg/kg caffeine) during 1 hour.<sup>46</sup> One 23-year-old chronic energy drink consumer had a myocardial infarction.<sup>46</sup>

### Physiologic Effects of the Ingredients in Energy Drinks

#### Caffeine Pharmacology and Physiology

Caffeine, the most commonly used psychoactive drug worldwide, may be the only psychoactive drug legally available over-the-counter to children and sold among food and beverage products.<sup>39,48</sup> Caffeine is an adenosine and benzodiazepine receptor antagonist, phosphodiesterase inhibitor, and central nervous system stimulant.<sup>29,38,49</sup> In healthy adults, a caffeine intake of  $\leq 400$  mg/day is considered safe; acute clinical toxicity begins at 1 g, and 5 to 10 g can be lethal.<sup>29</sup>

Physiologically, caffeine causes coronary and cerebral vasoconstriction, relaxes smooth muscle, stimulates skeletal muscle, has cardiac chronotropic and inotropic effects, reduces insulin sensitivity, and modulates gene expression in premature neo-

**FIGURE 3**

A, Cumulative probability curves of children (5–12 years old) consuming 1 to 4 retail units of energy drinks or energy shots in addition to baseline dietary exposure.<sup>46</sup> B, Cumulative probability curve for teenagers (13–19 years old) consuming 1 to 4 retail units of energy drinks or energy shots in addition to baseline dietary exposure.<sup>46</sup> C, Cumulative probability curve of young males (19–24 years old) consuming 1 to 4 retail units of energy drinks or energy shots in addition to baseline dietary exposure.<sup>46</sup> Caffeine-exposure units are mg/kg body weight per day. An adverse-effect level of 3 mg/kg body weight per day is shown as a reference point. The portion of each curve to the right of the adverse-effect level represents the proportion of the population group potentially at risk from adverse effects of caffeine. The exposure of any percentile may be read off the x-axis by extrapolating from the intersection of the selected percentile on the y-axis with the curve of 1, 2, 3, or 4 retail units consumed; cumulative probability = 0.2 represents the 20th percentile, 0.4 = 40th percentile, etc. Reproduced with permission from David Crowe, manager of consumer communications for the New Zealand Food Safety Authority.

nates.<sup>9,29,50–52</sup> Large amounts of caffeine increase urine flow and sweat excretion and alter blood electrolyte levels.<sup>11,53</sup> Although caffeine is a mild diuretic, consumption of  $\leq 500$  mg/day does not cause dehydration or chronic water imbalance.<sup>54,55</sup>

Caffeine is a ventilatory stimulant with anti-inflammatory and bronchoprotective effects.<sup>56</sup> Caffeine has been linked to dyspnea on exertion from central and peripheral chemoreceptor stimulation.<sup>56</sup> In addition, increased breathing work may divert blood flow away from locomotor muscles and negate any ergogenic advantage.<sup>56</sup> Caffeine's cardiovascular effects include decreased heart rate from stimulation of medullary vagal nuclei and increased blood pressure.<sup>24,57–61</sup>

Adults who consume low-to-moderate amounts of caffeine (1–3 mg/kg or 12.5–100 mg/day) have improved exercise endurance, cognition, reaction time, and mood with sleep deprivation.<sup>9,24,56,62</sup> However, these studies typically involve habitual caffeine consumers, and results reflect withdrawal-symptom reversal.<sup>58</sup>

Consuming 4 to 12 mg/kg of caffeine has been associated with undesirable symptoms, including anxiety and jitteriness.<sup>63</sup> Headache and fatigue, common withdrawal symptoms, can occur after short-term, high-dose use.<sup>64</sup> Caffeine intoxication is a clinical syndrome of nervousness, irritability, anxiety, insomnia, tremor, tachycardia, palpitations, and upset stomach.<sup>6,7,9,14,26,65</sup> Additional adverse effects include vomiting and abdominal pain, hypokalemia, hallucinations, increased intracranial pressure, cerebral edema, stroke, paralysis, rhabdomyolysis, altered consciousness, rigidity, seizures, arrhythmias, and death.<sup>1,2,8,29,48</sup>

Caffeine intakes of  $>300$  mg/day have been associated with miscarriage and low birth weight.<sup>38,66,67</sup> Long-term caffeine consumption relates to a lower

**TABLE 6** American Association of Poison Control Centers' Data on Caffeine Toxicity, 2006–2008<sup>47</sup>

Year	Total calls to PCCs to Report Caffeine Toxicity, n	Calls That Reported Caffeine Toxicity in Children <6 y old, n (% of Total Calls)	Calls That Reported Caffeine Toxicity in 6- to 19-Year-Olds, n (% of Total Calls)	Calls That Reported Caffeine Toxicity in Adults (>19 y old), n (% of Total Calls)	Patients Subsequently Treated, n (% of Total Calls)	Patients With Moderately Severe Symptoms, n (% of Total Calls)	Patients With Life-Threatening Effects, n (% of Total Calls)	Deaths, n (% of Total Calls)
2008	4852	1208 (24.9)	1170 (24.1)	1090 (22.5)	1281 (26.4)	470 (9.7)	11 (0.2)	1 (0.02)
2007	5448	1176 (21.6)	1328 (24.4)	1404 (25.8)	1561 (28.7)	544 (10.0)	16 (0.3)	1 (0.02)
2006	5696	1247 (21.9)	1427 (25.1)	1427 (25.1)	1799 (31.6)	654 (11.5)	18 (0.3)	1 (0.02)

PCC indicates poison control center.

risk of Parkinson disease and a slower age-related cognitive decline.<sup>58</sup>

#### *Effects of Caffeine in Children and Adolescents*

Adolescent and child caffeine consumption should not exceed 100 mg/day and 2.5 mg/kg per day, respectively.<sup>7,38,63</sup> For example, 8 oz of Red Bull (Fuschl am See, Austria) provides 77 mg of caffeine, or 1.1 mg/kg for a 70-kg male or 2.2 mg/kg for a 35-kg preteen.<sup>40</sup> Whether the effects of caffeine in adults can be generalized to children remains unclear.<sup>63</sup> In a study of 26 boys and 26 men, the same dose of caffeine affected blood pressure similarly, but heart rate was significantly lowered in boys, whereas there was no effect on heart rate in men.<sup>68</sup> Boys also exhibited more increased motor activity and speech rates and decreased reaction time than did men.<sup>69</sup>

Caffeine can improve attention, but it also increases blood pressure and sleep disturbances in children.<sup>24,63,70,71</sup> After cessation in children who habitually consume caffeine, attention decreases and reaction time increases transiently.<sup>24,39</sup> Similarly, reaction time has been shown to decrease as the dose of caffeine in children increases.<sup>24</sup>

In a study of 9- to 11-year-olds with habitual (mean intake: 109 mg/day) and low (mean intake: 12 mg/day) caffeine consumption given 50 mg of caffeine after overnight abstention, habitual caffeine users reported withdrawal-symptom (headache and

dulled cognition) reversal. The children who did not habitually consume caffeine reported no marked changes in cognitive performance, alertness, or headache.<sup>63</sup>

Caffeine may affect future food and beverage preferences by acting on the developing child's brain reward-and-addiction center; this effect may be gender specific.<sup>5</sup> A study of 12- to 17-year-olds revealed that boys found caffeinated soda more reinforcing than did girls regardless of usual caffeine consumption.<sup>72</sup>

#### **Physiologic Effects of Other Ingredients in Energy Drinks and Potential Synergistic Effects**

Popular media and case reports have associated adverse events with energy drink consumption (Appendix). Yet, few studies have examined the physiologic effects of individual ingredients or potential synergistic effects; furthermore, results of experimental studies have been inconclusive and occasionally contradictory.<sup>24,25,59,73</sup>

Some studies of adults revealed improved mental alertness, reaction times, and concentration with energy drinks<sup>59,74</sup>; others revealed no improvement compared with caffeine or glucose alone.<sup>73</sup> One study of 14 young adults compared a complete energy drink mixture to the glucose fraction, the caffeine fraction, and the herbal fraction.<sup>9,59</sup> Although individual components did not enhance cognition, the combined ingredients did.<sup>9,59</sup> Caffeine

and taurine combined may synergistically decrease heart rate initially; one study found that 70 minutes after consumption, heart rate returned to normal and blood pressure increased.<sup>25,75</sup> Taurine similarly produced a reflex bradycardia when injected into the rat cerebroventricular system.<sup>75</sup> Another study of 15 healthy young adults in a 7-day trial in which they consumed 500 mL of an energy drink each day with 160 mg of caffeine and 2000 mg of taurine, reported an average increase in systolic blood pressure of 9 to 10 mm Hg and an average increased heart rate of 5 to 7 beats per minute 4 hours after consumption.<sup>25,38</sup>

Caffeine- and taurine-containing beverages increased left atrial contractility in 13 athletes, thereby increasing left ventricular end-diastolic volume and stroke volume.<sup>76</sup> The caffeine-only group showed no changes in left ventricular function.<sup>76</sup> Taurine may cause this increase in stroke volume by suppressing sympathetic nervous stimulation and influencing calcium stores in cardiac muscle.<sup>8</sup> Results of human and animal studies have suggested that long-term taurine exposure may cause hypoglycemia<sup>25</sup> but a decreased risk of coronary heart disease.<sup>77</sup> In animal experiments, taurine also has shown anticonvulsive and epileptogenic properties.<sup>25</sup>

Among 50 young adults who drank one sugar-free energy drink, hematologic and vascular effects included increased platelet aggregation and

mean arterial pressure and a decrease in endothelial function.<sup>78</sup> Guarana has antiplatelet aggregation properties in vitro, but how it functions physiologically in energy drinks is unknown.<sup>79</sup> A study of 20 healthy subjects revealed that caffeinated espresso had no effects on endothelial function.<sup>80</sup> Caffeine alone did not affect platelet function.<sup>81</sup>

Ginseng, a common ingredient in many energy drinks, may lower blood glucose levels, but its actions in energy drinks are unclear.<sup>82</sup>

### Potential Problems of Energy Drinks Among Children and Adolescents

#### *Cardiovascular Effects of Energy Drinks on Children and Adolescents*

High doses of caffeine may exacerbate cardiac conditions for which stimulants are contraindicated.<sup>17,18,83–86</sup> Of particular concern are ion channelopathies and hypertrophic cardiomyopathy, the most prevalent genetic cardiomyopathy in children and young adults, because of the risk of hypertension, syncope, arrhythmias, and sudden death.<sup>11,86,87</sup>

#### *Effects of Energy Drinks on Children and Adolescents With ADHD*

ADHD occurs in 8% to 16% of US school-aged children and may be more prevalent in children with heart disease.<sup>88,89</sup> Some 2.5 million US children take stimulants for ADHD, which may increase heart rate and blood pressure.<sup>89–91</sup> Children with ADHD have higher rates of substance abuse, including the abuse of caffeine, which blocks the A2A adenosine receptors and thereby enhances the dopamine effect at the D2 dopamine receptor, similarly to the way guanfacine works for ADHD.<sup>92,93</sup> For the subpopulation with methylphenidate cardiotoxicity, energy drink use may increase cardiac events.<sup>95,96</sup> As with the ADHD stimulants, the com-

bined effects of energy drinks and antidepressants are unknown.<sup>94</sup>

#### *Energy Drink Use in Children and Adolescents With Eating Disorders*

Children and adolescents with eating disorders, especially anorexia nervosa, may regularly consume high amounts of caffeine to counter caloric-restriction-associated fatigue, suppress appetite, and produce looser stools and some diuresis.<sup>97–100</sup> Given that children and adolescents with eating disorders have a propensity for cardiac morbidity/mortality and electrolyte disorders, consumption of high-caffeine energy drinks may put them at further risk for cardiac dysrhythmias and intracardiac conduction abnormalities.<sup>97–99</sup>

#### *Effects on Caloric Intake and Diabetes*

Because obesity is epidemic, caloric increases from energy drink consumption become important. Additional calories may increase blood pressure, blood glucose levels, BMI, calcium deficiency, dental problems, depression, and low self-esteem.<sup>4,101,102</sup> Sugar and caffeine may also synergistically increase postprandial hyperglycemia, which is of concern for children with diabetes.<sup>38,51,52</sup>

#### *Effects on Bone Mineralization*

Early adolescence is the time of maximal calcium deposition in bone, and caffeine interferes with intestinal calcium absorption.<sup>103,104</sup> It remains controversial whether caffeine itself has the most marked effect on bone acquisition during adolescence or whether replacement of milk intake by caffeinated beverages is the leading contributor.<sup>103,104</sup>

### Marketing of Energy Drinks

Youth-targeted marketing strategies date to 1987 when Red Bull was introduced in Austria.<sup>100</sup> When it took 5 years to get permission to export Red Bull to Germany, rumors about its legality and dangerous effects helped

fuel its popularity, and it became known as “speed in a can,” “liquid cocaine,” and a “legal drug.”<sup>100</sup>

Energy drink marketing strategies include sporting event and athlete sponsorships, alcohol-alternative promotion, and product placement in media (including Facebook and video games) oriented to children, adolescents, and young adults.<sup>43,105</sup> Newer alcoholic energy drinks, the cans of which resemble the nonalcoholic counterparts, target risk-taking youth.<sup>43</sup>

Contrasting with brand design is the voluntary fine-print warning label on some products, which state that they may not be safe for children, those who are sensitive to caffeine, or for pregnant or nursing women.<sup>105–107</sup>

### Regulation of Energy Drinks

The FDA imposes a limit of 71 mg of caffeine per 12 fl oz of soda.<sup>1,2,6</sup> Energy drink manufacturers may circumvent this limit by claiming that their drinks are “natural dietary supplements.”<sup>1,2</sup> Thus, safety determinations of energy drinks are made solely by the manufacturers, and there are no requirements for testing, warning labels, or restriction against sales or consumption by minors.<sup>1–3</sup> In contrast, over-the-counter dedicated caffeine stimulants (eg, No-Doz [Novartis Consumer Health, Parsippany, NJ]) must list the minimum age for purchase (12 years), adverse effects, cautionary notes, recommended dose, and the total daily recommended dose of caffeine. In November 2009, the FDA asked manufacturers of alcoholic energy drinks to prove their safety.<sup>108</sup> The US Senate is considering a bill that would require supplement manufacturers to register annually with the FDA and allow FDA recalls of supplements suspected of being unsafe. Ingredients may also be restricted to those that have already been approved by the FDA.<sup>109</sup>

**TABLE 7** National and International Energy Drink Regulations

Country	Bans on Energy Drinks	Restrictions	Proposed or Attempted Regulation
Argentina	—	—	Senate has proposed banning energy drinks in nightclubs <sup>5</sup>
Australia	Recently banned 5 energy drinks on the basis of a caffeine content of >320 mg/L <sup>116</sup>	—	Classifying energy drinks as pharmaceutical products, which are regulated, has been proposed <sup>116</sup>
Canada	—	Requires warning labels, recommends a maximum daily consumption amount, and advises against mixing energy drinks with alcohol until further research has been conducted <sup>25</sup>	—
Denmark	Prohibits energy drinks entirely <sup>5,25</sup>	—	—
European Food Safety Authority	—	Beverages that contain >150 mg/L caffeine should be labeled "high caffeine content" and the exact amount present indicated on the label <sup>46</sup>	—
France	—	—	Banned Red Bull but recently removed the ban after assessment by the European Food Safety Authority <sup>6</sup>
Germany	11 of 16 German states banned Red Bull Cola because of trace amounts of cocaine <sup>111</sup>	—	Stricter regulations on warning labels have been requested by the government <sup>32</sup> ; the German Federal Institute for Risk Assessment recommends that energy shots be banned because of the high risk of overdose <sup>38</sup>
Ireland	—	—	Ireland is reviewing energy drink safety; Ireland's food-safety board has recommended that energy drinks be labeled as unsuitable for children <16 y old and that a ban be placed on the promotion of Red Bull in sporting events and in combination with alcohol <sup>118,120</sup>
Netherlands	—	—	Reviewed energy drink safety and declared no risk <sup>118,120</sup>
Norway	—	Energy drinks can only be sold in pharmacies <sup>5,25</sup>	—
Sweden	—	Sales to children <15 y are banned; warning labels about consuming high caffeine after exercise and mixing energy drinks with alcohol are also present <sup>5</sup>	—
Finland	—	—	Drinks that contain >150 mg/L of caffeine must be labeled "high caffeine content" and also must be labeled "not recommended for children, pregnant women, or people sensitive to caffeine" <sup>46</sup> ; energy drinks must also state the maximum amount to be used daily <sup>46</sup>
Turkey	Ban on all high-caffeine energy drinks <sup>5,118</sup>	—	—
United Kingdom	—	—	The UK's Committee on Toxicity investigated Red Bull and determined that it was safe for the general public but that children <16 y old or people sensitive to caffeine should avoid drinks with high caffeine content <sup>5,31</sup>
Uruguay	—	—	—
United States	Prohibits energy drinks entirely <sup>121</sup>	The FDA has listed caffeine as generally recognized as safe in concentrations of <200 mg/kg; in November 2009, the FDA announced plans to examine the safety of caffeinated alcoholic beverages <sup>46</sup>	In 2008, Kentucky, Maine, and Michigan introduced legislation that would ban the sale of highly caffeinated drinks to children <18 y old, but the bills were defeated <sup>30</sup> ; California is considering a bill to require special labels on alcoholic beverages to avoid confusion with nonalcoholic beverages <sup>43</sup>

Regulatory controversies also extend internationally (Table 7). When France banned Red Bull, the manufacturers challenged the ban through the European Commission, which determined that the caffeine and taurine concentrations in energy drinks had not been proven to be health risks and ordered France to lift the ban; the European Food Safety Authority has encouraged international data-pooling to better assess risks in children, adolescents, and young adults.<sup>33,110</sup> In 2008, authorities in Germany, Hong Kong, and Taiwan detected 0.13 µg per can of cocaine (average) in Red Bull Cola. Red Bull manufacturers insisted that active cocaine was removed from the coca leaf during processing and that the extract was used for flavoring. However, 11 of 16 German states banned the product.<sup>111</sup>

## CONCLUSIONS

On the basis of this review, we conclude that (1) energy drinks have no therapeutic benefit, and both the known and unknown pharmacology of various ingredients, combined with reports of toxicity, suggest that these drinks may put some children at risk for serious adverse health effects<sup>11,16,24,25,38</sup>; (2) typically, energy drinks contain high levels of caffeine, taurine, and guarana, which have stimulant properties and cardiac and hematologic activity,<sup>7,8,11</sup> but manufacturers claim that energy drinks are nutritional supplements, which shields them from the caffeine limits imposed on sodas and the safety testing and labeling required of pharmaceuticals<sup>7,8,11</sup>; (3) other ingredients vary, are understudied, and are not regulated; (4) youth-aimed marketing and risk-taking adolescent developmental tendencies combine to increase overdose potential; (5) high consumption

is suggested by self-report surveys but is underdocumented in children (deleterious associations with energy drink consumption have been reported globally in case reports and popular media<sup>7,8,11,25,31,38</sup>); and (6) interactions between compounds, additive and dose-dependent effects, long-term consequences, and dangers associated with risky behavior in children remain to be determined.<sup>5,14,25,38</sup>

## EDUCATIONAL, RESEARCH, AND REGULATORY RECOMMENDATIONS

In the short-term, pediatric health care providers need to be aware of energy drink consumption by children, adolescents, and young adults and the potentially dangerous consequences of inappropriate use.<sup>112</sup> Diet and substance-use histories should include screening for episodic/chronic energy drink consumption, both alone and with alcohol. Screening is especially important for athletes, children with high-risk behaviors, certain health conditions (eg, seizures, diabetes, hypertension, cardiac abnormalities), and children with behavioral changes, anxiety, poor nutrition, or sleep disturbances.<sup>11</sup>

For most children, adolescents, and young adults, safe levels of consumption have not been established. Yet, heavy use may be harmful or interact with medications and cause untoward adverse effects. Health care providers should educate families and children at risk for the potential adverse effects of energy drinks.

Routine high school athletic physicals do not identify everyone at risk for sudden cardiac death.<sup>11,113</sup> Children with cardiac conditions should be counseled regarding the risks of caffeine-containing products, including irregular heart rhythms, syncope, dysrhythmias, and sudden death.<sup>17,18,85</sup>

Community partners, including schools, athletic groups, and regulatory bodies, also need to promote risk awareness.<sup>113</sup> The fourth edition of the “Preparticipation Physical Evaluation” monograph will feature a revamped health questionnaire focused on cardiac health problems that may be exacerbated by physical activity; thus, adding questions about stimulant use, including energy drink consumption, becomes important.<sup>113</sup>

Long-term research objectives should aim to better define maximum safe doses, the effects of chronic use, and effects in at-risk populations (eg, those with preexisting medical conditions, those who consume energy drinks during and after exercise, or those who consume them in combination with alcohol), and better documentation and tracking of adverse health effects.<sup>47</sup> Unless research establishes energy drink safety in children and adolescents, regulation, as with tobacco, alcohol, and prescription medications, is prudent.<sup>11</sup>

This approach is essential for reducing morbidity and mortality, encouraging research, and supporting families of children and young adults at risk for energy drink overdose, behavioral changes, and acute/chronic health consequences.

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**APPENDIX** Representative Sample of Adverse Events Reported in Association With Nonalcoholic Energy Drink Consumption

Source of Information	No. and of Age Patients	Previous Health Conditions	Symptoms	Reported Association With Energy Drink	Ref No.
Journal articles/ case reports	One 25-y-old woman	Mitral valve prolapse	Unknown	Drank a bottle of Race 2005 Energy Blast with guarana and ginseng on the day that she had a cardiac arrest; the autopsy and toxicological screen results were negative except for a caffeine concentration of 19 mg/L in arterial blood	29
	One 25-y-old man	None reported	Generalized seizures on 2 occasions over 4 mo; the seizures did not reoccur within 6 mo after abstaining from energy drinks	Reportedly drank energy drinks on an empty stomach; he reported consuming two 24-oz energy drinks 30–60 min before the seizure	27
	One 31-y-old man	None reported	Rhabdomyolysis and acute kidney failure with tubular necrosis	Active football referee drank 3 cans of Red Bull before a 3000-m competition; the authors stated that the taurine could have caused the rhabdomyolysis from hyperosmolarity because the distance was relatively short compared with his normal training	25 and 38
	One 43-y-old man	Paranoid-type schizophrenia and alcohol dependence in full, sustained remission	6-wk history of worsening paranoia, delusions, and agitation resulting in hospitalization	Started drinking energy drinks 2 wk before becoming symptomatic; consumption increased to 8–10 cans per d; the cessation of caffeine reportedly improved symptoms	114
	One 47-y-old man	None reported	Delusions and paranoia; the psychosis resolved within 7 wk after reducing caffeine consumption	High caffeine intake	13
	2 patients	Migraine headaches	Seizures	In 1 case, the energy drink was consumed on an empty stomach; in the other case, caffeine tablets were also consumed with the energy drink	26
	2 depressed patients and 1 patient with no psychiatric illness One young professional volleyball player	Started on ginseng for several months	Unknown	Mania, which resolved after stopping taking ginseng	8
	7 high school students	None reported	Developed orthostatic intolerance, postural tachycardia, and syncope, which resolved after energy drink consumption was stopped	4–5 cans of Red Bull per d	75
Newspaper articles	4 middle school students	None reported	All transported to the hospital with tachycardia, hypertension, paresthesias, diaphoresis, jitters/anxiety, hypokalemia and hypersglycemia were diagnosed in the emergency department	All 4 shared 1 can of Redline energy drink	16
	One teenaged boy	None reported	Shortness of breath, heart palpitations, nausea; 2 students were treated in a hospital	Several Redline energy drinks (250 mg of caffeine per 8-oz serving) per d	32
Marin Institute	One 14-y-old girl	Diabetes	Severe stomach pain for ~2 mo; endoscopic findings included severe inflammation, bleeding, and ulcerations in the duodenum	SPIKE Shooter	43
	One 18-y-old girl	None reported	2 d after drinking 1 can of SPIKE Shooter, she was hospitalized for a seizure	Died after sharing 4 cans of Red Bull with friends and then playing basketball	43

**APPENDIX** Continued

Source of Information	No. and of Age Patients	Previous Health Conditions	Symptoms	Reported Association With Energy Drink	Ref No.
Online news sources	One 14-y-old girl	Diabetes	Seizure	Reportedly drank 1 can of an energy drink before the seizure	25 and 38
	One 7-y-old girl	None reported	Collapsed at the finish of a track race and was rushed to the emergency department after reporting chest pain and fatigue	Regularly skipped breakfast and drank 2 or 3 cans of Red Bull	1
	One 28-y-old man	None reported	The man reportedly drank energy drinks and then engaged in the strenuous physical activity of motocross; he subsequently died from a cardiac arrest, presumably from coronary vasospasm caused by the energy drinks	Unknown energy drink unspecified but large numbers of energy drinks that contained high levels of caffeine and taurine were consumed	28
	One 47-y-old man	None reported	"I thought I was having a heart attack. I thought I was going to die." The next day he reported feeling sore and exhausted from the experience	Two 8-oz cans of VPX Redline	119